

REMARKS

Upon entry of this amendment, claims 1- 7 and 11-13 are pending in the instant application. Claims 1 - 3, and 5 - 7 have been amended herein. Claims 8-10 have been canceled without prejudice or disclaimer. Claims 11-13 have been added. Support for the claim amendments presented herein is found throughout the specification and in the claims as originally filed. Accordingly, no new matter has been added by these amendments.

The Examiner indicated that claims 3, 4, 6, 8, and 10 were withdrawn from consideration. Claims 8 and 10 were drawn to the unelected invention of Group II. These withdrawn claims are canceled herein.

Applicants note, however, that claims 3, 4, and 6 were not subject to the restriction requirement. In response to a species election, Applicants elected the sub-generic species of compounds of formula II, wherein R¹ and R² are hydrogen; the species 3-benzyl-oxazol-3-ium salts; and the indication arteriosclerosis. Applicants also note that the Examiner has stated that no art was found for the elected species, and the search was expanded. *See* Office Action at page 2. Therefore, Applicants do not believe claims 3, 4, and 6 should be withdrawn from consideration.

CLAIM OBJECTIONS

The Examiner has objected to claims 1 and 5 for reciting the punctuation "{...}" and "...)". Applicants have amended claims 1 and 5 to delete "{...}" and "...)" and to recite appropriate punctuation numeral ",". Applicants submit that this objection is now moot and should be withdrawn.

CLAIM REJECTIONS

CLAIM REJECTION UNDER 35 U.S.C. §112

Claim 9 was rejected under 35 U.S.C. §112 as indefinite. Applicants have herewith cancelled claim 9 without prejudice or disclaimer. Accordingly, this objection is moot and should be withdrawn.

CLAIM REJECTION UNDER 35 U.S.C. §101

Claim 9 was rejected under 35 U.S.C. §101. Applicants have herewith cancelled claim 9 without prejudice or disclaimer. Accordingly, this objection is moot and should be withdrawn.

CLAIM REJECTION UNDER 35 U.S.C. §103

Claims 1, 2, 5, 7 and 9 were rejected under 35 U.S.C. §103 as being unpatentable over Dominianni and Yen, (1989) J. Med. Chem. 32:2301-2306 ("Dominianni"). The Examiner states that Dominianni discloses the compound 3-[2-(3,5-dimethoxyphenyl)-2-oxoethyl]-oxazolium bromide, and that this compound has hypoglycemic activity and may be useful as an oral hypoglycemic agent. See Office Action at page 4. According to the Examiner, "it would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the compound of Dominianni as claimed because one of ordinary skill in the art would not expect minor substitutions to affect the overall properties of the compound." (Office Action at page 4). Applicants traverse.

Applicants have herewith cancelled claim 9 without prejudice or disclaimer. Accordingly, this objection as applied to this claim is moot and should be withdrawn.

The present invention relates to oxazolium compounds that are described as agents that inhibit the formation of or break AGE-mediated protein crosslinks. Specifically, claim 1 relates to oxazolium compounds of formula II. Dominianni relates to compounds that may be useful in treating diabetes by reducing blood glucose (hypoglycemic agents). Moreover, as acknowledged by the Examiner, Dominianni fails to specifically disclose a compound where one or more of the methoxy substituents are absent, or that there may be additional substituents added. (See Office Action at page 4).

Applicants submit that there is no motivation based on structure or proposed use to modify the compounds of Dominianni to arrive at the compounds of the instant invention.

First, Dominianni does not teach or suggest *oxazolium* compounds. Rather, Dominianni relates to phenacylimidazolium halides (see, e.g., Dominianni title, abstract). Dominianni discloses the synthesis and testing for hypoglycemic activity of 59 compounds, only one of which is an oxazolium compound, Compound 6, 3-[2-(3,5-dimethoxyphenyl)-2-oxoethyl]-oxazolium bromide. See Dominianni Table 1, pages 2302-2303. There is no teaching or suggestion in Dominianni to generate modified *oxazolium* compounds, in order to arrive at the compounds of the invention. In fact, Dominianni teaches away from making oxazolium compounds. Dominianni indicates that "[o]f the compounds examined, only 1-3, 26-27, 30, 23-33, 38-40, 42, 47, 48, and 52 could be regarded as active, producing reductions of blood glucose of 20-40%." See Dominianni p. 2304. Compound 6, the only oxazolium compound mentioned

in the reference, is not described as an active compound. Furthermore, Dominianni states that “of the heterocycles examined, hypoglycemic activity was confined to the imidazoles and even within the imidazoles our results place severe constraints on structure I.” See Dominianni p. 2304. Thus, one of ordinary skill in the art would not be motivated to modify the Dominianni oxazolium compound.

Second, the indications treated by the compounds of the invention include those that are characterized by the formation of AGE-mediated crosslinks. Such indications include, for example, fibrotic diseases, arteriosclerosis and other diseases of the cardiovascular system, macular degeneration, tissue damage as a result of dialysis, renal disease, diabetic neuropathy, diabetic retinopathy, and systolic hypertension (*e.g.*, as seen in diabetic patients). See, *e.g.*, pages 1 and 9-20 of the instant application.

Dominianni relates to hypoglycemic agents. Any teaching of the use of the compounds disclosed in Dominianni to treat diabetes relates to using these compounds to lower blood glucose levels. Indeed, Dominianni states that “the phenylacylimidazolium salts may be operating through a novel hypoglycemic mechanism.” There is no teaching or suggestion in Dominianni of the use of the disclosed compounds to inhibit the formation of or to break AGE-mediated protein crosslinks.

Thus, Applicants contend that one of ordinary skill in the art would not be motivated to modify the compounds taught by Dominianni in order to achieve the compounds of the claimed invention. Likewise, as noted above, Dominianni fails to teach or suggest all of the limitations of the claimed invention. Therefore, claim 1 is not obvious in view of Dominianni.

Moreover, claims 2, 5, and 7 each depend from claim 1. As such, they necessarily contain all of the limitations of claim 1. Therefore, for the reasons articulated above, Applicants contend that these claims are also not obvious in view of Dominianni.

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SERIAL NUMBER: 10/037,447

CONCLUSION

On the basis of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance. If there are any questions regarding these remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

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